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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,361	MCGRATH, KEVIN	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-15 and 17-52* is/are pending in the application.

4a) Of the above claim(s) *30-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-15,17-29 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-7, 9-15 and 17-52 are pending.

Applicant's amendment filed 4 January 2005, which cancels claims 8 and 16, amends claims 2-3, 5, 9-11, 13, 17-19, 21, 27 and 29, and adds claims 50-52, has been entered. Claims 30-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention (see Office action mailed 3 September 2004). The subject matter of claims 50-52 are drawn to the elected invention. Thus, the pending claims 1-7, 9-15, 17-29 and 50-52 are examined in this office action. It is of note that Group II includes claims 30-49.

Please note that ground of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Election/restriction

On page 15 of the response filed 4 January 2005, applicant discusses the issue regarding claims 19-29 (drawn to pharmaceutical composition) which link product claims 1-29 and method claims 30-49, and submit that the linking claims must be examined with the invention elected. The applicants' argument is found to be unpersuasive because the pharmaceutical composition comprising the claimed peptide of formula II are not considered as the linking claims, and because the method claims are not related to the pharmaceutical composition of claim 19-29 but rather an inhibitor of hypoxia-inducible factor 1 (HIF-1) of the Group I claims, i.e., the method claims are not linked by claims 19-29.

In the 3rd paragraph of page 15, applicant further asserts that when searching the pharmaceutical composition, examiner will be perforce searching the method claims that are directed to use of the Group I composition (elected) due to intended use of the pharmaceutical composition thereof; and thus, applicant requests for withdrawal of the restriction requirement. The applicant's argument is found to be unpersuasive because Group I (the composition claims) and Group II (the method claims) are related as product and process of use which is patentably distinct (see the office action mailed 26 May 2004), and because the intended use of the pharmaceutical composition is not set forth in the claims and thus will not be searched. Hence, the requirement is deemed proper and is therefore made FINAL.

Claim Rejection under 35 USC 101

35 U.S.C. §101 states:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7, 9-15, 17-18 and 50-51 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 2-3 and 11, and the dependent claims thereto, as written, do not sufficiently distinguish over polypeptides as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed polypeptide and the naturally occurring polypeptides. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

The applicants' response to the rejection under 35 USC 101

The response filed 4 January 2005 asserts that since the claimed peptides have been sequenced, i.e., have been taken out of their natural environment and purified to a degree sufficient to permit sequencing (see page 16). The applicants' argument is found to be not persuasive because the claims as written do not expressly indicate the claimed peptide has been isolated or/and sequenced. Note that the recited sequence identity does not necessarily reflect the peptide has been actually isolated and sequenced; it can be a result of supposition or speculation in the absence of factual indicia to the contrary.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-7, 9-15, 17-18 and 50-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite because the claim recitation "at least 90% identity to SEQ ID NO:4" does not make sense. Note that the SEQ ID NO:4 peptide consists of only 8 amino acid residues; and thus, the minimal % of structural alteration would be change in one residue, i.e., 87.5%. Note that although the open-ended language "comprising" would render the peptide longer than SEQ ID NO:4, in the absence of reciting a sequence identifier for said peptide, the recitation "90% identity to SEQ ID NO:4" is considered indefinite. See also claims 17 and 25.

Also, claim 9 recites "the inhibitor of claim 3 wherein the peptide comprises..."; the recitation is indefinite because claim 3 from which claim 9 depends recites the close language "...consisting of..." contrary to the open-ended "...comprises..." of claim 9 . Note that the scope of dependent claim should not be broader than that of the independent claim therefrom; otherwise, it would render the said dependent claim indefinite. Further, claim 9 is indefinite in that both SEQ ID NOs:4 and 7 do not read on the formula II of claim 3 (see methionine residue 1 in SEQ ID NO:4 and methionine residue 6 in SEQ ID NO:7). and 10

Claims 3 and 11 appear to be duplicate; claim 50 and 51, which depend from claim 3 and claim 1, respectively, are duplicate. Also, claims 4, 5, 6 and 7 appear to be duplicate over claims 12, 13, 14 and 15, respectively, which render the claims indefinite. The dependent claims are also rejected.

Claim 12 recites the limitation "the activator of ..."; there is no antecedent basis for this limitation in claim 11 from which claim 12 depends. Does the "activator" refer to stimulator of transcription of vascular endothelial growth factor (VEGF) through inhibiting HIF-α1 ubiquitination as set forth in the instant abstract? See also claims 13-15 and 17-18.

The applicants' response to the rejection under 35 USC 112, second paragraph

On page 16, the response filed 4 January 2005 argues that the claim 9 peptide may be a part of a longer sequence due to "comprising" recitation in the claim, and thus, infers that claim 9 is not indefinite. The applicant's argument is found to be unpersuasive because a sequence identifier (SEQ ID NO:_) is necessary for determining said sequence identity (i.e., 90% identity to..."); however, claim 9 does not set forth such the peptide sequence with said sequence

identifier which is longer than SEQ ID NO:4 so that the sequence identity of 90% to SEQ ID NO:4 or 7 in claim 9 can be determined.

Claim Rejections - 35 USC § 112, the first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to describe the polypeptide variant that has 90% sequence identity (subsequences) to the full-length polypeptide of SEQ ID NO:7 (claim 1), and that the polypeptide variant has an activity. These variants comprising deletion/truncation, substitution, addition and/or insertion mutations. Note that, for SEQ ID NO:7, 10% amino acid alteration counts for at least three amino acid mutations). The current disclosure fails to provide a representative number of the variants (e.g., ~ 10% amino acid variations, any substitutions, deletions or /and insertions) that retain the activity of full-length sequence of SEQ ID NO: 7. Applicants were therefore not in a possession of the claimed variant polypeptides. Therefore, the specification lacks written description of the claimed polypeptide.

Applicants may wish to amend the claims to additionally list a specific and measurable activity or function that these variables must have so that one skilled in the art can recognize

when they are in possession of a polypeptide having at least 90% identity to SEQ ID NO: 7 and having a specific function, for example.

The applicants' response to the rejection under 35 USC 112, first paragraph

On pages 17-18, the response filed 4 January 2005 argues that one skilled in the art would recognize that Applicant was in possession of active variant polypeptide of SEQ ID NO:7 as the knowledge of persons skilled in this art is high which is applicable to the SEQ ID NO:7 sequence. The applicants' argument is found to be unpersuasive because the synthesized SEQ ID NO:7 peptide consists of the two functional domains: (1) residues 1-11 (YGRKKRRQRRR) which facilitates translocation of polypeptide into cytoplasm, and (2) residues 12-30 (DLDLEMLAP*YIPMDDFQL, wherein "P*" represents hydroxylated proline residue) which is a domain mediating oxygen-dependent degradation of HIF-1α (see the bridging paragraph on pages 25-26 of the specification). Hence, any structural modification into theses two **key** domains (the second line from the bottom, page 25) would result in inactive variant peptide in the absence of factual evidence to the contrary. This would not allow the variant peptide to retain the activity of inhibiting ubiquitination of HIF-1α of the unmodified SEQ ID NO:7 peptide. Therefore, the skilled artisan is not in possession of the variant polypeptide of SEQ ID NO:7.

The following is the new ground of rejection.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims 3-7, 9-15, 17-26, 28-29 and 50-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Ratclifffe, P. et al. (WO 00/69908) as is evidenced by the known facts that reticulocyte lysate contains endogenous prolyl hydroxylase (HPHase) activity (the right column, page 1337 of Bruick R. K. et al. reference (*Science* (2001) 294, 1337-1340)), and that proline, e.g., residue 564, of HIF-1 α is hydroxylated (modified) with the lysate (see ref. 25 on page 472 of Jaakkola et al. (*Science* (April 2001) 292, 468-472)).

It is of note that claims 9-10 appear to be not dependent from claim 3 because neither SEQ ID NO:4 nor SEQ ID NO:7 reads on formula II of claim 3. Thus, claims 9 and 10 are taken to be independent from claim 3. For the same reason, claims 17 and 18 are taken to be independent from claim 11 as recited.

In the patent claim 12, Ratclifffe et al. disclose an isolated polypeptide consisting of LAPYIPMD (SEQ ID NO:1) which reads on the formula II peptide of the instant claim 3. In Example(n) on page 40, Ratclifffe et al. teach the peptide is incubated with reticulocyte lysate, or, is produced in a cell free system, i.e., reticulocyte lysate (see page 14, lines 12-18, and page 37, lines 7-11). Because said lysate has HPHase activity as taught by Bruick et al. (see page 1337, the right column, lines 17-23), and because the HPHase catalyses hydroxylation of proline 564 as taught by Jaakkola et al. (see abstract), the proline residue 3 (*equivalent to residue 9 of the instant formula II*) in the above mentioned polypeptide is hydroxylated when the polypeptide is expressed using the reticulocyte lysate. Thus, at time when the invention is made, one skilled in the art would have inevitably had the isolated pro-hydroxylated peptide in hand. Hence, the Ratclifffe's teaching anticipate the instant claims 3 and 9-10.

In the above-mentioned SEQ ID NO:1 peptide, acidic amino acid is aspartic acid, which anticipated the instant claim 4.

In the above-mentioned SEQ ID NO:1 peptide, aliphatic amino acids are leucine, alanine and isoleucine which anticipated the instant claim 5.

In the above-mentioned SEQ ID NO:1 peptide, polar amino acid is tyrosine, which anticipated the instant claim 6.

In the above-mentioned SEQ ID NO:1 peptide, apolar amino acid is methionine, which anticipated the instant claim 7.

The above Ratclifffe et al. teachings anticipate the instant claims 11-15 and 17-18 because they are duplicate over claims 3- 7 and 9-10, respectively.

On pages 21-23, Ratclifffe et al. teach a pharmaceutical composition comprising the above said polypeptide and a pharmaceutical acceptable carrier, which anticipates the instant claim 19.

The above Ratclifffe et al. teachings with respect to (i) aliphatic amino acids are leucine; (ii) polar amino acid is tyrosine; and (iii) apolar amino acid is methionine meet the limitations set forth in claims 20-23.

Ratclifffe et al. teach that, in the above-mentioned SEQ ID NO:1 peptide, aromatic amino acid is tyrosine, which anticipates that instant claim 24.

In the patent claims 12-13, Ratclifffe et al. disclose the polypeptide "DLDLEMLAPYIPMDDDFQL" (SEQ ID NO:8), which has 100% sequence identity to the instant SEQ ID NO:5. The Ratclifffe et al. disclosure anticipates the instant claims 25-26.

On page 22, Ratclifffe et al. teach that administering formulation is in form of cream or transdermal patches and the like, indicating a sustained release formulation, which anticipates the instant claim 28.

Claims 27 and 29 are also included in the rejection because use of the composition for "administered in conjunction with a wound dressing" (claim 27) and "with a surgical implant (claim 29) is considered to have little patentable weight as the composition will not be altered by said use.

In the Ratclifffe's peptide of SEQ ID NO:8 "DLDLEMLAPYIPMDDDFQL", residues 12 and 13 which is equivalent to residues 12 and 13 of the instant formula I) are proline and methionine, respectively, which anticipates the instant claims 50-51.

Further, Ratclifffe et al. teach that in the SEQ ID NO:8 polypeptide, residue 17 is phenylalanine, which anticipates the instant claim 52.

The claims 9-10 and 17-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Jaakkola et al. (*Science* (April 2001) 292, 468-472).

It is of note that claims 9-10 appear to be not dependent from claim 3 because neither SEQ ID NO:4 nor SEQ ID NO:7 reads on formula II of claim 3. Thus, claims 9 and 10 are taken to be independent from claim 3. For the same reason, claims 17 and 18 are taken to be independent from claim 11 as recited.

On page 470, the second to the last paragraph at the left column, Jaakkola et al. teach a synthesized peptide, which is an inhibitor of HIF-1α ubiquitination, consisting of "DLDLEMLAP*YIPMDDDFQL" (see "HIP-1α (556-574) sequence in Figure 3) wherein "P* "

stands for hydroxylated proline residue 564. The peptide segment "MLAP*YIPM" reads on the instant SEQ ID NO:4. The Jaakkola's teaching anticipates the instant claims 9 and 10.

Because claims 17 and 18 are duplicate over claims 9 and 10, respectively (see the above-stated rejection under 35 USC 112, second paragraph), for the same reason set forth above, the Jaakkola's teaching anticipates the instant claims 17 and 18.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-29 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jaakkola et al. (*Science* (April 2001) 292, 468-472) and taken with Semenza, G. L. (US Pat. No. 6124131).

Jaakkola et. al. teach an inhibitor of HIF-1α ubiquitination comprising the sequence consisting of "DLDLEMLAP*YIPMDDDFQL" (see "HIP-1α (556-574) sequence in Figure 3) wherein the 9th residue, i.e., proline 564 equivalent to *proline residue 9* of the instant formula II is hydroxylated. The Jaakkola' peptide "DLDLEMLAP*YIPMDDDFQL" meets the limitation set forth for formula I, as applied to the instant claim 19.

Since the above mentioned peptide "DLDLEMLAP*YIPMDDDFQL" has 100% sequence identity to the instant SEQ ID NO:5, the Jaakkola et al. teaching is applied to the instant claims 25 and 26.

The Jaakkola's peptide shows that acidic residue of said peptide is aspartic acid, as applied to the instant claim 20.

The Jaakkola's peptide shows Jaakkola et al. teach that aliphatic residue of said peptide is alanine and/or leucine, as applied to the instant claim 21.

The Jaakkola's peptide shows that polar residue of said peptide is tyrosine, as applied to the instant claim 22.

The Jaakkola's peptide shows that apolar residue of said peptide is methionine, and/or proline, as applied to the instant claim 23.

The Jaakkola's peptide shows that aromatic residue of said peptide is phenylalanine and tyrosine, as applied to the instant claim 24.

Also, Jaakkola et al. teach that residues 567 and 568, which are equivalent to residues 12 and 13 of the instant formula II, are proline and methionine, which meets the limitation set forth in the instant claim 52.

Yet, Jaakkola et al. do not expressly teach pharmaceutical composition comprising the above said peptide.

On columns 19-20, Semenza et al. teach a pharmaceutical composition comprising HIF-1α polypeptide that comprises the peptide of sequence "DLDLEMLAPYIPMD" (see the patent SEQ ID NO:1, residues 556-569) wherein residues 7 to 14 of said sequence read on the instant formula II except that proline (residue 9 of said sequence) is not hydroxylated. The Semenza et al. teaching is applied to the instant claims 19-26 and 52.

On column 20, lines 23-24, Semenza et al. teach that the pharmaceutical composition is administered by sustained release systems (formulations), which is applied to the instant claim

28.

On column 19, lines 56-58, Semenza et al. teach that the pharmaceutical composition is administered by parenteral route or as implants, which is applied to the instant claim 29.

Claim 27 is also included in the rejection because use of the composition for "wound dressing" is considered to have no patentable weight as the composition will not be altered by said use.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the pharmaceutical composition comprising the peptide comprising von Hippel-Lindau tumor suppressor (pVHL) binding domain (see abstract of Jaakkola's reference), i.e., "DLDLEMLAP*YIPMDDDFQL". One skilled in the art would have been motivated to do this because:

(i) the HIF-1α peptide plays a key role in tumor growth and angiogenesis, as taught by Jaakkola et al. (see page 468, the 1st paragraph);

(ii) proline 564 (hydroxylated proline) is critical for HIF-1α interaction with the tumor suppressor pVHL, as taught by Jaakkola et al. (see page 469); the hydroxylation of the proline residue *inhibits or reduces* degradation of the tumor *suppressor* by ubiquitin-dependent proteolytic pathway in vivo. This would promotes treatment of tumorigenesis; and,

(iii) Semenza et al. has taught the pharmaceutical composition formulated with a HIF-1α polypeptide (see columns 19-20), and potential therapeutic application of the HIF-1α polypeptide that comprises the Jaakkola's peptide (see columns 14-19).

Thus, having been motivated by the above reference teachings, one skilled in the art would have readily formulated the pharmaceutical composition comprising the peptide stated

above. Therefore, the claimed invention would have been *prima facie* obvious at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.
Art Unit 1653, Examiner
February 10, 205

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER